REMARKS

Claims 22-30 are rejected under 35 U.S.C. § 112, first paragraph because of an alleged failure of the specification to enable a person skilled in the relevant art to make and use the invention commensurate with the scope of the claims. Applicants believe the rejection should be withdrawn for the reasons stated below.

The Examiner alleges that the specification fails to adequately describe the genus of compounds to be used in the methods of the invention. In the instant case, the specification describes a number of compounds that may be used in accordance with the claimed invention (see, *e.g.*, the specification at pages 26-28). Applicants respectfully remind the Examiner that an applicant is not required to disclose every species that is encompassed by their claims even in an unpredictable art. *In re Angstadt*, 537 F.2d 498 (CCPA 1976). Applicants have disclosed representative examples of known compounds that define members of the genus that can be used in the claimed methods, for example, cyclosporin A, a mitochondrial calcium blocker (*see, e.g.*, the specification at pages 26-28, last paragraph). Furthermore, the specification demonstrates that cyclosporin A was able to reduce HBV DNA replication in cytoplasmic core particles by 15 fold compared to untreated controls (*see, e.g.*, the specification at page 72, lines 16-20, and also in Figure 10A). The specification also provides guidance to distinguish members of the genus. In particular, the specification defines two unifying characteristics of compounds of the invention. First, useful members of the genus are described as those that inhibit HBV replication. Second, such compounds are also described as calcium antagonists. Applicants contend that the specification clearly identifies compounds useful in the claimed method, and enables one skilled in the art to identify other compounds that may be used in accordance with the invention. Therefore, Applicants have enabled the claims under the standard set forth by the Federal Circuit.

In the present application, Applicants are not claiming the compounds themselves, but rather, a new use for existing compounds and uses of new compounds, having the same or similar properties. Applicants respectfully point out that the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process for using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). In the instant case, the specification provides methods for the identification of such compounds possessing the desired properties (*i.e.*, inhibition of HBV replication) through the use of *in vitro* assays (*see, e.g.*, page 43-52 of the present

specification). Applicants assert that one of skill in the art could easily subject candidate compounds to the *in vitro* assays of the invention to discern genus members from the non-genus members. Using these criteria, the identification of any compound as inside the genus can easily be determined.

Furthermore, the Examiner contends that the specification does not provide guidance to one skilled in the art regarding the types of compounds encompassed by the claimed methods because the specification does not describe how cytosolic calcium concentration affects HBV replication. Applicants contend there is no requirement that the mechanism through which the invention works be known. (*see, Exxon Chemical Patents, Inc. v. Lubrizol Corp.* 77 F.3d 450 at 456).

> An inventor need not understand the scientific mechanism in order to place an invention into the patent system. (*see, Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed.Cir.1989) (observing that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"); *Fromson v. AdvanceOffset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed.Cir.1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.").

Rather, Applicants have shown the viral activities critical to supporting the HBV life cycle, *i.e.*, HBV replication and infection require elevated cytosolic calcium levels (*see, e.g.*, page 80, line 19 to page 81, line 9 and page 82, lines 1-24 of the instant specification). Based on these data, one of skill in the art would recognize that HBV replication could be effectively prevented by inhibiting cytosolic calcium levels. As such, Applicants assert that one of skill in the art would understand the types of the compounds encompassed by the claimed invention when reading the claims in light of the specification.

The Examiner also contends that the Applicant has not adequately described the genus of compounds that should be investigated because an art recognized animal model has not been utilized to determine if any or all of the compounds are able to lower cytosolic calcium levels and inhibit HBV replication. However, in the instant application, Applicants have applied the art recognized model, *i.e.*, the model recognized in the field of HBV, to determine if compounds, already known to lower cytosolic calcium levels, can inhibit HBV replication. In the instant case, the art based model for studying HBV replication is a cell-based model, as described in the instant specification (*see, e.g.*, Section 5.5.1 of the present

specification). Applicants remind the Examiner that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate (*see*, M.P.E.P. § 2164.02, Feb. 2003 revision of original 8th ed.).

In the instant case, the relevant art is that related to human hepatitis B virus. At the time of the invention, none of the animal systems were universally accepted as animal models of HBV disease. Instead, cell-based assays were used as more reliable predictions of efficacy for treating HBV infection (*see*, Sprinzl *et al.*, 2001, J. Virol. 75:5108-5118 (*Spinzl*) (attached hereto as Exhibit A) at page 5109). *Sprinzl* describes the adenovirus-mediated transfer of HBV genomes into cells in culture as an art recognized method to study HBV infection. Thus, the art related to HBV at the time of the invention recognized such cell-based assays as an accepted model for HBV replication because animal models were not readily available (*see, e.g., Sprinzl*, column 2 at page 5108). As such, one skilled in the art related to the invention would recognize a cell-based assay as being a reasonably predictive art accepted model for HBV replication. Thus, contrary to the Examiner's contention, the Applicants have utilized an art accepted model to determine whether compounds already known to lower cytosolic calcium levels fall inside the genus of the claimed invention, *i.e.*, that such compounds inhibit HBV replication.

The Examiner further alleges that the instant claims are not enabled because the specification provides no guidance on how to solve the problems associated with systemic administration of calcium modulators to patients. In response, the Applicants first point out that there have been a number of calcium antagonists that have been approved for use as drugs in humans, including those identified by the instant specification as encompassed by the claimed invention, *e.g.*, amlodipine, felodipine, isradipine, verapimil, bepridil, diltiazem, nifedipine and nimodipine (*see*, the specification at page 27, last paragraph). (*see also*, Abernethy and Schwartz, 1999, New England Journal of Medicine. 341:1447-57 (ed.: Wood, A.) attached hereto as Exhibit B (*Abernethy*)). *Abernethy* provides clinical dosing information for eight compounds that have been identified in the instant specification as calcium antagonists that can be used safely in humans (*see*, Table 1 on page 1449 of *Abernethy*). These compounds have already been approved and deemed safe for human use by the Food and Drug Administration (FDA), the entity that the United States Congress has authorized to ensure the safety and efficacy of drugs that are proposed for use in humans. Thus, a number of the calcium antagonists identified by the specification as encompassed by the claimed invention, have already been approved by the FDA as safe and

efficacious for administration to humans. Therefore, while Applicants are under no obligation to demonstrate the invention as completely safe [1], this "standard" of safety has obviously been met in the instant case and the rejection should be withdrawn. Applicants believe that the Examiner's concern regarding the detrimental effects of the compounds of the invention has been obviated, and as such, the pending claims are enabled.

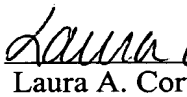
Applicants assert that in light of the foregoing, the full scope of the claims have been enabled by the present specification. Applicants have clearly described the relationship between the claimed compounds and the methods of the invention as well as exemplified the methods of the invention in great detail, using an art recognized model. Applicants earnestly request that the rejection of the claims under 35 U.S.C. § 112 be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of this application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: October 21, 2003



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[1] The requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug or therapeutic. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Indeed, the M.P.E.P. clearly sets forth that "[t]he applicant need not demonstrate that the invention is completely safe" (*see, e.g.*, M.P.E.P. § 2164.01(c) citing M.P.E.P. § 2107.01 and § 2107.03).